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10/053,230	01/16/2002	Xianqiang Li	26757-706	3906

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EXAMINER	
CHAKRABARTI, ARUN K	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/053,230	Applicant(s) Li
	Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 12, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Status of the Application

1. The amendment received on June 12, 2003 has been entered. Claims 1-40 have been amended. New claims 41 and 42 have been added.

Claim Rejections - 35 USC § 103

2 The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-10, 13-21, 22-39 and 41-42 are rejected under 35 U.S.C. 103(a) over O'Hare et al. (PCT International Publication Number WO 00/08182) (February 17, 2000) in view of Kain et al. (U.S. Patent 6,306,600 B1) (October 23, 2001).

O'Hare et al. teaches a method for selecting cells based on whether the cells express a short-lived protein (Abstract and Claims 1-7), the method comprising:

taking a library of cells, each cell in the library expressing a fusion protein comprising a reporter protein and a protein encoded by a sequence from a cDNA library derived from a s sample of cells, the sequence from the cDNA library varying within the cell library (Page 5, line 25 to page 7, line 12 and Figure 1);

modifying a rate of protein expression or degradation by cells in the library (Figure 1, lines 3-4 and Page 10, lines 10-31);

and

selecting a population of cells from the library of cells based on the population of cells having different reporter signal intensities than other cells in the library, the normalized reporter signal intensity comprising a reporter signal from the fusion protein normalized relative to a reporter signal from the first reporter protein, the difference being indicative of the population of cells expressing shorter lived fusion proteins than the fusion proteins expressed by the other cells in the library (Figure 1, line 6, and Page 10, line 31 to page 11, line 17).

O'Hare et al. teaches a method, wherein the reporter protein is a green fluorescent protein (Claim 1 and 6 and Page 5, line 25 to page 7, line 12 and Figures 1-2).

O'Hare et al inherently teaches a method, wherein protein expression is inhibited and selecting a population of the cells is based on the selected population of cells having a lower (less

than half) or higher (more than twice) reporter signal intensity than the other cells after modifying the rate of protein degradation (Figure 2 and Page 11, line 1 to page 12, line 6).

O'Hare et al. teaches a method, wherein the selected population of the cells are subjected to one or more additional rounds of selection, each round of selection comprising modifying a rate of protein expression or degradation by the cells, and selecting a further subpopulation of the cells based on whether the cells have different reporter signal intensities than the other cells (Page 7, line 21 to page 8, line 3).

O'Hare et al. teaches a method, wherein the selected population of the cells are subjected to one or more additional rounds of selection such that at least one round of selection comprises inhibiting protein expression and at least one round of selection comprises inhibiting protein degradation (Page 7, line 21 to page 8, line 3).

O'Hare et al. teaches a method, wherein the selected population of the cells are further selected, at least partially, by culturing cells separately and individually monitoring how the reporter signal of each cell culture changes, using a fluorescent plate reader in response to protein synthesis or protein degradation being inhibited (Page 9, line 15 to page 10, line 34).

O'Hare et al. teaches a method, wherein the method further comprises determining the nucleic acid sequences and inherently the protein sequences of the fusion proteins of the selected cells (Figure 2 and Page 11, lines 4-27).

O'Hare et al. teaches a method, wherein the method further comprises analyzing whether a portion of the fusion protein encoded by the sequence from the cDNA library is short-lived when expressed independent of the reporter protein (Page 9, lines 22-29).

O'Hare et al. teaches a method step of partitioning the library of cells into populations of cells based on an intensity of a reporter signal from the fusion protein such that cells partitioned into a given population have a reporter signal within a desired range of reporter signal intensity (Figure 1 and Page 10, line 10 to page 12, line 23).

O'Hare et al. teaches a method, wherein screening the transduced or transfected cells for cells which express the fusion protein is based on detection of the reporter protein (Figure 1 and Page 11, first two paragraphs).

O'Hare et al does not teach the method, wherein a fusion protein is expressed in each cell.

Kain et al. teaches the method, wherein a fusion protein is expressed in each cell (Figures 5-6).

O'Hare et al does not teach the method of inhibiting further expression of the fusion protein to allow the expressed fusion protein to degrade in the cell.

Kain et al. teaches the method of inhibiting further expression of the fusion protein to allow the expressed fusion protein to degrade in the cell (Example 6, Column 10, line 29 to Column 11, line 29 and Figure 4).

O'Hare et al does not teach the method, wherein the further synthesis of the fusion protein is inhibited by adding cycloheximide in the cell.

Kain et al. teaches the method, wherein the further synthesis of the fusion protein is inhibited by adding cycloheximide in the cell (Example 6, Column 10, line 29 to Column 11, line 29 and Figure 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method of inhibiting further expression of the fusion protein to allow the expressed fusion protein to degrade in the cell of Kain et al in the method for selecting cells of O'Hare et al. since Kain et al states, "Further, the reporter gene of the present invention can be linked with different enhancer elements and used to monitor diverse biological processes such as heat response, response to heavy metals, glucocoticoid activation or response to cAMP. In particular, destabilized EGFP is useful for studying developmental processes where genes are transiently expressed, dynamics of protein transport, localization of proteins within cells, and periodic and cyclical expression of genes that control unique biological phenomena such as circadian rhythms (Column 4, lines 37-46) ". An ordinary practitioner would have been motivated to substitute and combine the method of inhibiting further expression of the fusion protein to allow the expressed fusion protein to degrade in the cell of Kain et al in the method for selecting cells of O'Hare et al. in order to achieve the express advantages, as noted by Kain et al., of an invention which provides the reporter gene that can be linked with different enhancer elements and used to monitor diverse biological processes such as heat response, response to heavy metals, glucocoticoid activation or response to cAMP and in particular, provides destabilized EGFP that is useful for studying developmental processes

where genes are transiently expressed, dynamics of protein transport, localization of proteins within cells, and periodic and cyclical expression of genes that control unique biological phenomena such as circadian rhythms.

O'Hare et al. in view of Kain et al does not teach the method, wherein the signal intensity is equal or less than a half-log interval of fluorescence or a given population of cells has a modal brightness that differs from another population by a factor of at least 3 or screening the cells into at least four population of cells.

However, it is *prima facie* obvious that selection of the specific signal intensity having a modal brightness that differs from another population by a factor of at least 3 represents or screening the cells into some specific number of population of cells represents routine optimization with regard to sequence, length and compositions of the proteins and the genetic make-up of the cells being screened, which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the signal intensity and the number of population of cells selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the

results should be considered unexpected in any way as compared to the closest prior art.

4. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) over O'Hare et al. (PCT International Publication Number WO 00/08182) (February 17, 2000) in view of Kain et al. (U.S. Patent 6,306,600 B1) (October 23, 2001) further in view of Bachmair et al. (Science, (October 10, 1986), Vol. 234, pages 179-186).

O'Hare et al. in view of Kain et al. teaches the method of claims 1-10, 13-21, 22-39 and 41-42 as described above including immunoprecipitating the expressed fusion protein with ant-GFP antisera and analyzing the immunoprecipitate by SDS-PAGE.

O'Hare et al in view of Kain et al. does not teach the method wherein analysis of the fusion protein of the selected cells is carried out by a pulse-chase analysis by radiolabelling the expressed fusion protein and analyzing the immunoprecipitate by autoradiography.

Bachmair et al. teach the method wherein analysis of the fusion protein of the selected cells is carried out by a pulse-chase analysis by radiolabelling the expressed fusion protein and analyzing the immunoprecipitate by autoradiography (Figures 2, 4 and 5 and page 182, last two lines of second column to line 8 of page 183, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein analysis of the fusion protein of the selected cells is carried out by a pulse-chase analysis of Bachmair et al in the method for selecting cells of O'Hare et al. in view of Kain et al. since Bachmair et al states, "Thus the recognition of an amino-terminal residue in a protein may mediate both the metabolic stability

of the protein and the potential for regulation of its stability (Abstract, last sentence) ". An ordinary practitioner would have been motivated to substitute and combine the method, wherein analysis of the fusion protein of the selected cells is carried out by a pulse-chase analysis of Bachmair et al in the method for selecting cells of O'Hare et al in view of Kain et al. in order to achieve the express advantages, as noted by Bachmair et al., of an invention which provides the recognition of an amino-terminal residue in a protein may mediate both the metabolic stability of the protein and the potential for regulation of its stability.

5. Claim 40 is rejected under 35 U.S.C. 103(a) over O'Hare et al. (PCT International Publication Number WO 00/08182) (February 17, 2000) in view of Kain et al. (U.S. Patent 6,306,600 B1) (October 23, 2001) further in view of Dantuma et al. (Nature Biotechnology, (May 18, 2000), Vol. 18, pages 538-543).

O'Hare et al. in view of Kain et al. teaches the method of claims 1-10, 13-21, 22-39 and 41-42 as described above.

O'Hare et al in view of Kain et al. does not teach the method wherein screening is performed using a flow cytometer.

Dantuma et al. teach the method wherein screening is performed using a flow cytometer (Figure 4 and Experimental Protocol Section, Page 542, Microscopy, flow cytometry, and fluorometry Subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to substitute and combine the method, wherein screening is performed using a flow cytometer of Dantuma et al in the method for selecting cells of O'Hare et al. in view of Kain et al. since Dantuma et al states, "These reporters provide a new powerful tool for elucidation of the ubiquitin/proteasome pathway and for high throughput screening of compounds that selectively modify proteolysis in vivo (Abstract, last sentence) ". An ordinary practitioner would have been motivated to substitute and combine the method, wherein screening is performed using a flow cytometer of Dantuma et al in the method for selecting cells of O'Hare et al. in view of Kain et al. in order to achieve the express advantages, as noted by Dantuma et al., of an invention which provides a new powerful tool for elucidation of the ubiquitin/proteasome pathway and for high throughput screening of compounds that selectively modify proteolysis in vivo.

Response to Amendment

6. In response to amendment, all previous 102 (b) and 103(a) rejections have been withdrawn. However, new 103(a) rejections have been included.

Response to Arguments

7. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the LIE Chantae Dessau whose telephone number is (703) 605-1237.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center

numbers for this art unit 1634 is (703) 746-4979. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti
Patent Examiner
Art Unit 1634

GARY BENZION, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

August 15, 2003